

# **INTEGRATIVE MEDICINE RESEARCH: CONTEXT AND PRIORITIES**

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The responsibility for the content of this paper rests with the authors and does not necessarily represent the views or endorsement of the Institute of Medicine or its committees and convening bodies. The paper is one of several commissioned by the Institute of Medicine as background for the Summit on Integrative Medicine and the Health of the Public. Reflective of the varied range of issues and interpretations related to integrative medicine, the papers developed represent a broad range of perspectives.

**ABSTRACT** *Integrative medicine research is important for the understanding of and effective, timely implementation of this new paradigm of health care. Integrative medicine is prospective and holistic, while patient-centered and personalized at the same time, focusing on health and well-being in addition to disease management. The scope of research thus extends beyond evaluation of specific therapies, including complementary and alternative medicine modalities, for safety and effectiveness in treating specific diseases. Integrative medicine research also includes evaluation of multi-modality whole system intervention, practitioner-patient relationship and partnership, patient goals and priorities in his sense of well-being, promotion of patient self-care and resilience, personalization of diagnostic and therapeutic measures to individual patients and the environmental/societal consequence of health care. In this paper, we describe the state of science of integrative medicine research, research needs, and the opportunities offered by cutting edge research tools. We will propose a framework for setting priorities in integrative medicine research, list areas for discussion, and pose a few questions on future research agenda.*

## INTRODUCTION

Integrative medicine refers to a new paradigm of health care that is prospective and holistic, while patient-centered and personalized at the same time, focusing on health and well-being, in addition to disease management. The *scope of research* within integrative medicine as discussed in this paper is not only the evaluation of specific Complementary and alternative medicine (CAM) therapies for safety and effectiveness in treating specific medical problems (the Institute of Medicine published its report *Complementary and Alternative Medicine in the United States* in 2005). Integrative medicine research also includes multidisciplinary whole systems interventions; clinician-patient interactions; patient goals and priorities; the value of meaning; patient self-care; environmental factors and social policies affecting health quality; and system factors affecting availability of resources that promote health, health behaviors, or health care. Research must also address patient-centered care in the context of family, culture, and community. The research agenda for integrative medicine is by nature broad and comprehensive, rather than being focused solely on the effects and mechanism of selected therapies.

There is a lack of a critical mass of research evidence about integrative medicine and the effect of this approach on health care; this lack hampers understanding and effective, timely implementation. One challenge for research even in the limited realm of therapeutic effectiveness concerns the definition of “effectiveness.” Is it simply a change of a physiological parameter like blood pressure or survival time? Or an improved overall sense of well-being? Or can there simultaneously be multiple definitions, multiple goals? Who should define them—policy makers, clinicians, patients, or families? Another challenge is that interventions in integrative medicine are often multi-faceted with complex unknown interactions among the components. Therapies delivered as a multi-factorial “system” rather than a simple treatment regimen present challenges to design studies that are rigorous yet provide results that are meaningful in real-life clinical practice. Similarly, while traditional biomedical research focuses on one particular disease outcome, integrative care often addresses multiple health concerns within a single individual; new research models may need to be developed to address the challenges inherent in many simultaneous treatments for multiple health concerns. For example, inclusion of all patient-important outcomes in consideration to create the best evidence has been incorporated in the Grades of Recommendation Assessment, Development and Evaluation Working Group (Guyatt et al., 2008).

These challenges offer a fertile ground for the development of innovations to advance science. In this paper, we describe the state of science of integrative medicine research, research needs, and the opportunities offered by cutting edge research tools. We will propose a framework for setting priorities in integrative

medicine research, list areas for discussion, and pose a few questions on the future research agenda.

**CONTEXT:  
STATE OF THE SCIENCE, RESEARCH NEEDS, AND INTEGRATION  
WITH CUTTING EDGE RESEARCH TOOLS**

**Research Methodology**

*Study Design*

Integrative medicine researchers have broadly adopted the paradigm of evidence based medicine (EBM)—the randomized controlled trial (RCT). There is no disagreement that the RCT method helps reduce multiple sources of bias. Although RCTs are often viewed as the gold standard, it is not possible to conduct RCTs for each research question we have, due to logistic, economic, or ethical concerns. RCTs do not include patients who do not fit rigorous entry criteria (such as those unwilling to be randomized), which limits generalizability. RCTs also only provide population or group estimates of *likely* outcomes rather than assurances of individual outcomes with treatment. While the strongest conclusions and inferences can be reached when there is concordance between research using different methods (e.g., RCT and prospective cohort methods), such concordance is not always found, such as the different conclusions reached by cohort versus RCT studies of hormone replacement therapy (Chlebowski et al., 2003; Wassertheil-Smoller et al., 2003), antioxidant supplements to prevent cancer (Bardia et al., 2008) or decreased risk of dementia/cancer in patients using statins (Shepherd et al., 2002). Observational studies have provided important insights such as the role of smoking, radiation, hormone levels, and high meat diets in the development of different kinds of cancer, lipids and coronary disease, hypertension and stroke, and sleeping position and sudden infant death syndrome (Rothwell and Bhatia, 2007). *Researchers need to recognize that different kinds of research serve complementary functions in developing balanced and mature evidence (Avorn, 2007).*

*Outcome Assessment Tools*

Optimal health in integrative medicine refers to a state of well-being of the whole person—physical, mental, social, and spiritual (Gaudet and Snyderman, 2002; Maizes and Caspi, 1999; Singer et al., 2005; Snyderman and Weil, 2002).

With this multi-dimensional definition of health in mind, outcome measurements in integrative medicine research would need to expand beyond reduction of a specific symptom or reversal of a specific disease process (Bell et al., 2002; Long, 2002).

Integrative medicine researchers can make use of outcome measurement methods developed in other disciplines of medicine, especially those emphasizing functional performance in addition to structural integrity and those taking into consideration the psychological and societal impact of disease (Coons et al., 2000), such as rheumatology (Ward, 2004), neurology (Miller and Kinkel, 2008; von Steinbuechel et al., 2005), geriatrics (Burns et al., 2000; Demers et al., 2000), rehabilitation (Andresen and Meyers, 2000; Donnelly and Carswell, 2002), and pain and palliative care (Turk et al., 2002). They form a foundation from which integrative medicine researchers can build a truly global outcome measurement system.

Another important aspect in outcome measurement is the role of the patient. In patient-centered care, what patients perceive is equally, or perhaps more, important than what physiological parameters tell us. Integral to this process is incorporating individual patient preferences in considering appropriate study outcomes (Guyatt et al., 2000). Information about patient preferences can be obtained from decision analyses, cost-effectiveness analyses, studies of social values, one-on-one interviews, focus groups, and interviews of citizen juries and other novel sources (Ryan et al., 2001). The value of patient-reported outcome measures is increasingly being recognized by the medical community (Clauser et al., 2007; Lipscomb et al., 2007). Integrative medicine researchers can incorporate what was learned into their own studies and develop new methods tailored to their own practice models (Hull et al., 2006; Sagar, 2008; Verhoef et al., 2006a).

### *Application of Information Technology*

The impact of information technology (IT) on integrative medicine is enormous. Easy and instant access to a vast amount of health-related information on the Internet via search engines such as Google and Wikis plays a large role in patients' senses of empowerment. This decentralization of information makes practitioners not the sole source of information. Meanwhile the information, not uncommonly inaccurate, false, or contradictory, overwhelms, confuses, and frustrates patients. On the other hand, information technology provides researchers with numerous tools which have not been utilized adequately.

IT can be used to enhance research in its capacity as a communication tool in many ways.

- 1) E-mails improve communications between providers and patients (Mandl et al., 1998; Roeder and Martin, 2000). Would email communications encourage a patient's stake in self-care, facilitate timely management of emerging medical problems, or reduce unnecessary utilization of health care resources? Would email communications help monitor patient responses and adverse events, improve patient compliance, and refine patient-centered outcome evaluation in clinical studies? These are interesting research questions.
- 2) Online support groups, bulletin boards, chat rooms, blogs, and social network sites are frequented by patients to exchange notes on their diseases and health care providers. These media, by their nature, are part of the social context of a patient health care experience. They can be used to learn patients' perspectives of the medical problems. Participation of providers in those discussions, medicolegal issues notwithstanding, could promote provider-patient partnership. They also serve a venue to reach a large number of patients eligible for research studies.
- 3) The raw computing power available to researchers has made certain previously impossible research feasible now. This is most obvious in bioinformatics and personalized medicine. IT enables the processing of the astronomical amount of information generated from genomic studies and establishing links between genomic variations and clinical outcomes.
- 4) Image processing technologies can be used to standardize and quantify some of the diagnostic techniques in traditional medicine. For example, image digitalization and analysis of the appearance of the tongue and complexion in Traditional Chinese Medicine would help eliminate evaluator biases (Dong et al., 2008; Pang et al., 2004; Zhang et al., 2005).
- 5) Web 2.0 technology (Giustini, 2006) provides a social, collective, and collaborative platform that simplifies data creation, integration, sharing, and reuse. It fosters collective intelligence to create and discover new knowledge (Zhang et al., 2008b). When expanded beyond the research community, it also presents a platform in education to other health care providers and the public (Bender et al., 2008; Eysenbach, 2008).
- 6) Finally, artificial intelligence has potentials in contributing to whole-system research (Patel et al., 2008; Ramesh et al., 2004). Many traditional medical systems rely on pattern recognition for diagnosis. For example, diagnoses in Ayurvedic medicine or Traditional Chinese Medicine are established by a constellation of findings during patient interviews and physical examinations that are seemingly unrelated when viewed through the eyes of Western medicine. However, recognition of those patterns may represent empirical knowledge on clinical manifestations of some yet nondelineated pathophysiological links (Zhang et al., 2008a).

## **Epidemiological Studies**

The large numbers of epidemiological studies in integrative medicine have been on the use of CAM (Barnes et al., 2004; Eisenberg et al., 1998; Eisenberg et al., 1993; Ritchie et al., 2005; Wilson et al., 2006; Yussman et al., 2004). Several population based surveys have included a CAM component including: the 1999 and 2002 National Health Interview Survey; 1994 Robert Wood Johnson Foundation National Access to Care Survey; 2001 Michigan State Behavioral Risk Factor Surveillance System; 1997 National Health Expenditures Survey; 2001-2003 National Comorbidity Survey Replication; and 1996 Medical Expenditure Panel Survey (Ni et al., 2002; Paramore, 1997; Rafferty et al., 2002; Ritchie et al., 2005; Wang et al., 2005). Much of what we know about CAM utilization comes from these surveys, and continued collection of this data is essential to further understanding of the field. Research describing integrative medicine programs including how they were established, the services offered, and the training and research projects they are conducting are emerging (Boon and Kachan, 2008; Deng, 2008; Katz et al., 2003).

It would be beneficial to the field if a standardized survey could be created to gather data about CAM and integrative medicine use. This standardized survey could then be made publicly available to all researchers conducting population-based surveys. This may be the most efficient way to collect descriptive data about integrative medicine's utilization, cost-effectiveness, and the characteristics and satisfaction of the individuals who use it. Continuation of the CAM supplement to the National Health Interview Survey (NHIS) is a minimal requirement to maintain an understanding of the utilization of CAM in the United States. *Efforts should be made to review and update the supplemental questions in the NHIS to be sure that they reflect changes and trends in the field, such as including questions specifically about integrative medicine and CAM treatments recommended by conventional providers.*

## **Basic Science Research**

### *Mechanistic Studies of Specific CAM Modalities*

Mechanistic studies have begun to elucidate biomedical mechanisms to explain clinical effects of CAM therapies. For biologically based therapies such as botanicals, the research generally identifies the (presumed) active constituent(s) of the study agents and the physiological pathways through which those constituents affect physical systems (Ribnicky et al., 2008). This approach is highlighted in the NIH Botanical Research Centers Program, where researchers “identify and char-

acterize botanicals, assess bioavailability and bioactivity, explore mechanisms of action, conduct preclinical and clinical evaluations, and help select botanicals to be tested in clinical trials” (Barnes et al., 2008b). Isolating active compounds and their derivatives has led to the development of many pharmaceuticals currently used in clinical practice, such as the taxanes and camptothecins in cancer chemotherapy (Wall and Wani, 1995). However, the complex composition of botanicals may contain multiple compounds that synergize for a greater total activity than individual constituents (Raskin et al., 2002; Rong et al., 2008; Schmidt et al., 2008; Ye et al., 2007). Studying natural products with complex composition presents challenges, such as standardization and quality control, unknown active constituents, multiple potential biological targets, and complex interactions among the constituents (Khan, 2006; Yeung et al., 2008). Newer experimental paradigms are needed to assess the differential effects of complex mixtures versus simple compounds. Similar to conventional pharmacotherapy, this research needs to also take into account the effects of secondary metabolites of botanicals on biological materials.

Mechanistic studies of energy medicine, manipulative practices, and mind-body therapies involve delineation of the physiological pathways modulated by them. For example, research in “psychoendoneuroimmunology,” focuses on an interdisciplinary study of interactions among behaviors, the conscious mind, the autonomic nervous system, hormones, and immune functions (Kiecolt-Glaser and Glaser, 1995; McEwen, 2007). Through such research, the relationships between stress and disease, especially stress and immune function, are being explored (Ehlert et al., 2001; Gaillard, 2001; Kiecolt-Glaser and Glaser, 1992; McEwen, 2008; Miller and Cohen, 2001). The neuroendocrine stress response and immune systems have a bidirectional relationship that can affect susceptibility to inflammatory diseases. Individual variability in neuroendocrine responsiveness may contribute towards the efficacy of mind-body therapies (Marques-Deak et al., 2005).

The brain plays a central role as a target of stress and stress therapy. Neuroplasticity, a dynamic process that constantly alters the neurochemical, structural, and functional components of the nervous system related to experience would be a worthwhile target to study with mind-body interventions. Some of the examples of the effect of mind-body approaches on brain structure include the increase in prefrontal cortex volume following cognitive behavioral therapies in patients with chronic fatigue syndrome (de Lange et al., 2008) and increase in prefrontal cortex and right insula volume with meditation (Lazar et al., 2005). The role of neurotrophins, particularly Brain Derived Neurotrophic Factor (BDNF) as a mediator for neuroplasticity is beginning to emerge and needs to be further characterized with respect to mind body intervention (Hennigan et al., 2007). The brain is a

malleable organ and the lack of resilience may be a key aspect of anxiety and mood disorders, as well as other systemic problems.

Like psychotherapy, many behavioral and mind-body interventions require active patient participation, which cannot be reproduced in animal studies. Advances in functional neuroimaging technology such as functional Magnetic Resonance Imaging (fMRI) or Positron Emission Tomography (PET) can demonstrate changes in activity in regions of the brain in real-time and enable us to study the complex neuronal matrix involved in real-world emotional and social experience (Eisenberger et al., 2007). The technology has been used to study mind-body therapies or energy-medicine modalities in recent years (Lewith et al., 2006). For example, anterior cingulate cortex and dorsolateral prefrontal areas appear involved in meditation (Cahn and Polich, 2006). Activities in the thalamus, insula, and cingulate cortex, areas involved in processing of pain signals, are modulated by meditation (Kakigi et al., 2005; Orme-Johnson et al., 2006) and acupuncture (Cho et al., 2006; Dhond et al., 2007). The specific neurobiologic changes that might mediate the placebo effect could offer innovative therapeutic insights. A recent example of this is the effect of placebo on endogenous opioid release in core affective brain regions (Wager et al., 2007). The efficacy of placebo effect on enhancing frontal modulation of nociceptive sensory and/or affect processing and individual variability in placebo responsiveness as a predictor of efficacy of mind-body interventions is an interesting area for future exploration (Benedetti et al., 2005; Oken, 2008).

Because physiological pathways are increasingly understood to be nonlinear and multidimensional, traditional laboratory approaches tend to be too simplistic to capture the complexity of real clinical situations. Advanced mathematical and statistical modeling techniques will be important to advance research in the complex systems of integrative medicine. Sensitive and noninvasive methods that can measure multiple biomarkers are likely to help identify pathways that may be selectively affected by different interventions. A good example of this strategy is the use of sweat patch method for measuring neural and immune biomarkers in sweat (Cizza et al., 2008; Marques-Deak et al., 2006).

### *Application of Genomic Science To Personalized Health Care*

Some technologies developed in genomic sciences can be harnessed to enhance integrative medicine research, in particular towards personalized health care. Genomics refers to the study of all the genes of a cell, or tissue, at the DNA (*genome*), mRNA (*transcriptome*), or protein (*proteome*) levels. It is well known that individuals respond differently to risk exposure and interventions. More knowledge of the DNA sequence of the human genome and the function of indi-

vidual genes and their variants makes it possible to identify individuals at risk for a particular medical condition or responsive to a particular intervention.

Variations at nearly 100 regions of the genome have been associated with an increased risk for diseases with a complex genetic background, such as diabetes, inflammatory bowel disease, cancer, and heart disease (Chanock and Hunter, 2008). For example, single nucleotide polymorphisms (SNPs) in a region of the long arm of chromosome 15 were identified as strongly associated with lung cancer (Amos et al., 2008; Hung et al., 2008; Thorgeirsson et al., 2008). This region contains nicotinic acetylcholine receptor subunit genes. Genetic variants in nicotinic receptor genes were found to be linked to nicotine dependence and smoking behavior, which may explain why some patients are particularly resistant to smoking cessation measures (Berrettini et al., 2008; Saccone et al., 2007).

Another example is how individuals respond differently to nutrients (*nutrigenomics*) (Trujillo et al., 2006). Individuals with one genetic variant of an intestinal fatty acid-binding protein gene have significantly greater decreases in plasma total and low-density lipoprotein (LDL)-cholesterol and apoB when consuming a diet rich in soluble fiber (Hegele et al., 1997). Better understanding of nutrigenomics would help us in understanding the “individuality” of one’s response to bioactive food components (Milner, 2008). The Institute of Medicine has held a workshop to review the state of nutritional genomics research and to provide guidance for further development and translation of this knowledge into nutrition practice and policy (Stover and Caudill, 2008).

The ever expanding database in *pharmacogenetics* helps us understand why individuals respond quite differently to the same biological intervention. For instance, the best responses to erlotinib treatment in patients with nonsmall-cell lung cancer are seen in those who have mutations in epidermal growth-factor receptor, the target of erlotinib (Rosell et al., 2006). Differences in response to drugs or dietary supplements may also come from varied metabolism (Kadiev et al., 2008). CYP2D6 is one of the major drug-metabolizing enzymes involved in converting codeine to morphine. CYP2D6 gene is highly polymorphic, with more than 100 allelic variants in the population. Depending on the allele combinations, a patient can be a poor, intermediate, extensive, or ultra-rapid metabolizer. Extensive metabolizers may have markedly increased risk of side effects while poor metabolizers would experience poor efficacy of the drug (Somogyi et al., 2007).

*Epigenetics* refers to the study of heritable changes in gene function that occur without a change in the DNA sequence (Riddihough and Pennisi, 2001). Such changes can occur via mechanisms such as DNA methylation, chromatin structural modifications, and RNA interference (Jenuwein and Allis, 2001; Okamura and Lai, 2008; Reik et al., 2001). Inspired by the Human Genome Project, researchers are working to provide high-resolution reference epigenome maps and speed progress in epigenetic research (the Alliance for the Human Epigenome and

Disease) (Jones, 2008). Epigenetics takes into consideration the effects of the environment on gene expression patterns that can be passed along to daughter cells, setting the stage for disease preventive interventions to have a lasting effect. For example, epigenetic alterations often are involved in the earliest stages of tumor progression, and usually precede genetic changes in the cell and tumor transformation (Toyota and Issa, 2005). These findings may lead to novel cancer prevention strategies early in the cancer pathogenesis process (Sawan et al., 2008), including use of botanical agents or nutritional approaches (Kirk et al., 2008).

Although these technologies are exciting and promising, they are expensive and require additional development before their results can be translated into effective clinical care. At this point, the science to make personalized treatment decisions is available at a level of confidence only for a handful of diseases. *Much work needs to be done to achieve the ideal of personalized integrative medicine based on genomic technologies.*

## **Clinical Research**

### *Therapeutic Clinical Trials and Meta-Analysis*

To date, the majority of clinical trials in the field of integrative medicine have focused on evaluating single components from the system for efficacy in treating a specific medical condition (e.g., St. John's Wort for depression, a specific set of acupuncture points for headaches, a protocol of chiropractic adjustments for low back pain, or melatonin for insomnia). It is beyond the scope of this paper to provide a summary of all the clinical trials conducted in the field, but a search of Medline resulted in nearly 6,500 randomized controlled trials under the medical subject heading of complementary therapies, which was only created in 2002. In some cases, there have been enough studies on a particular treatment and condition to result in a systematic review or meta-analysis (nearly 3,000 systematic reviews and 400 meta-analyses are found in Medline when using the complementary therapies subject heading). The Cochrane Database of Systematic Reviews has published more than 600 articles related to complementary therapies as of November 2008. Readers are referred to those reviews for a summary of findings in clinical trials (Bausewein et al., 2008; Bjelakovic et al., 2008; Dickinson et al., 2008; He et al., 2007; Horneber et al., 2008; Maratos et al., 2008; Priebe et al., 2008; Zhu et al., 2008).

A common limitation of several nonpharmacologic interventions is difficulty with blinding, with the related issue of finding a credible control intervention. Some of the approaches used in the fields of surgery and psychology that might be applicable here include blinding participants to the study hypothesis, use of

sham training approaches, sham procedures, similar attention-control interventions, and blinding of outcome assessors (Boutron et al., 2007). Incorporating elements of the CONSORT statement for the nonpharmacologic treatments at the time of clinical trial design might help with the quality of study design (Boutron et al., 2008). *Taking a broad, patient-centered approach and including mixed outcomes that evaluate the basic mechanisms (such as modern imaging studies) and combining them with safety, economic, and patient relevant outcomes data will likely increase the strength of the evidence even if the study can only be designed as a single-blind (investigator) trial.* A related issue is the importance of maintaining objective neutrality on the part of the investigators. This is particularly so for nonpharmacologic interventions because, for example, part of the effect of a treatment modality such as acupuncture part of the effect may be related to the context and process of Traditional Chinese Medicine (TCM) (Paterson and Dieppe, 2005).

Identification and inclusion of generalizable molecular markers that have been correlated with stress and are responsive to stress management (such as telomerase activity and telomere maintenance capacity in human immune-system cells) will likely increase the credibility of study findings and provide more objective surrogate outcome measures (Epel et al., 2004; Ornish et al., 2008). Incorporation of noninvasive methods to measure immune system outcome measures will not increase the disease burden while obtaining additional rich data (Cizza et al., 2008; Marques-Deak et al., 2006).

A challenging issue in studying biologically based therapies, such as dietary supplements, is an ability to secure a consistent study agent with multiple and sometimes unknown active constituents (Harkey et al., 2001). Careful selection of the study population and endpoints is crucial for the success of the trial. A structured, well thought out approach needs to be developed so that the limited resources available are optimally utilized for testing interventions with a high potential for efficacy (Vickers, 2007), particularly in light of several recent expensive negative trials with dietary supplements (Atwood et al., 2008; Bent et al., 2006; Clegg et al., 2006; Shelton et al., 2001; Taylor et al., 2003).

Attentions need to be paid to the scope and overall design of the study with the intent to balance internal validity with external generalizability. For example, for dietary supplements, phase I/II trials that might be helpful towards dose establishment and assessment of safety before embarking on expensive phase III trials (Vickers, 2006); Vickers et al., 2006). For mind-body, energy-based, and manual interventions, the initial focus should be on creating a structured and reproducible intervention, consistent with how they are practiced in real life along with an appropriate control group.

Combining data for a meta-analysis can be particularly challenging in the field of integrative medicine. For example, there are hundreds of forms of Qi Gong and

each is used traditionally for different reasons; there are several traditions of acupuncture and many different needling techniques; herbal preparations can vary greatly depending on the growing conditions and extraction methods. The appropriateness of merging such a diverse group of therapies in meta-analysis and the resultant conclusions is subject to debate.

### *Whole Systems Research and Multi-Modality Studies*

A new trend in integrative medicine research is the push for “whole systems” research, which strives to examine the effect of a multi-modality health care approach to provide individualized treatment, since this will more accurately evaluate the health care currently being provided to patients. There are several commentaries in the literature urging integrative medicine researchers to consider research methods beyond the RCT (Boon et al., 2007; Cardini et al., 2006; Fonnebo et al., 2007; Ritenbaugh et al., 2003). One example of whole systems research is the study by Ritenbaugh et al., who examined the effect of whole system TCM versus naturopathic medicine versus standard of care for the treatment of temporomandibular disorders (Ritenbaugh et al., 2008). In this study, improvement was seen in temporomandibular disorders when participants were randomized to whole systems treatment interventions beyond that seen in the standard care group (Ritenbaugh et al., 2008).

Several investigators have discussed the need to use more complex methods of analysis so that these systems of health care can be examined, rather than the efficacy of each part of the system (Bell and Koithan, 2006; Ritenbaugh et al., 2003; Verhoef et al., 2005). Some suggest using network and complex system analysis as methods for assessing whole systems research; however, it is critical for researchers interested in these methods to work with skilled biostatisticians experienced with these more complex statistical methods (Bell and Koithan, 2006). Verhoef et al. encourage researchers to add qualitative measures to studies because they can provide a source of data for unexpected outcomes and a way to measure the broader effects of a whole system, such as integrative medicine (Verhoef et al., 2005). It is important for researchers in the field of integrative medicine to consider the range of effects the treatments may have for patients, and thus to measure a broad area of outcomes in order to detect these effects.

## **Beyond Therapeutic Clinical Trials**

### *Individual Resilience and Hardiness*

Of the three variables in the triangle of disease causation (agent, host, and environment), host factors remain suboptimally addressed in modern medicine. Other medical systems consider strengthening the host as a primary focus. Resilience and hardiness refer to positive abilities and skills of an individual in response to stress and adversity (Rutter, 1987). In adults, the components of “hardiness” include: commitment (ability to find meaning in events); control (belief in internal locus of control); and challenge (belief that challenging experiences provide an opportunity for learning and growth) (Kobasa, 1979). In children, three correlates of resilience have been noted: (1) personality disposition (e.g., humor, critical thinking skills, problem solving skills, self discipline, internal locus of control, self-esteem, positive outlook, positive expectancies, and effectiveness in work, play, and love) (Luthar, 1991; Rutter, 1985, 1987; Werner, 1989); (2) family ties and cohesion; and (3) external support systems (Garmezy, 1993). Exposure to stress and traumatic events is common, but, not all of those exposed develop post traumatic stress disorder (PTSD) or other negative health outcomes. Hardiness is correlated with positive health outcomes (Bartone et al., 1989; Ford et al., 2000; Williams and Lawler, 2001). Individual aspects of resilience are also associated with positive outcomes (Livanou et al., 2002; Yi et al., 2008). For example, greater preevent internal locus of control prevents PTSD in women giving birth (Soet et al., 2003) and maintaining treatment gains for patients with PTSD. Resilience is thus an important concept in the fields of physical, mental, and spiritual health. *Additional research is needed to enhance understanding of hardiness or resilience factors that protect an individual from developing physical and emotional illness in the face of stress, to identify optimal strategies in developing resilience within integrative medicine, and to identify social factors that can be modified to support hardiness to promote public health.*

### *Social Factors and Practitioner-Patient Relationship*

Social support enhances resilience (Turner et al., 2003; Regehr et al., 2000; King et al., 1998; Perry et al., 1992). A strong network of friends was associated with improved survival in the elderly (Rodriguez-Laso et al., 2007; Giles et al., 2005). The effect of social support on physical health and longevity may be medi-

ated through improved depressive symptoms, perception of a better quality of life, better health care access, improved compliance with treatments, positive effects on the immune system, a sense of engagement, continued learning, and a feeling of purpose in life (Ciechanowski et al., 2004; Cohen et al., 2007; Reichstadt et al., 2007; Schwartz, 2005). Providing social support to others might have an even greater impact on survival than receiving social support (Brown et al., 2003). Practitioners can offer meaningful social support that enhances health outcomes (Fogarty et al., 1999; Ganz, 2008). When individuals become a caregiver of a family member with a chronic disease, it is important to assess the strain and burden of this role and provide support and coping strategies to help maintain wellness of the caregiver (Honea et al., 2008; Raina et al., 2004; Weitzner et al., 2000).

Integrative medicine emphasizes the importance of the *relationship* between practitioner and patient to achieve optimal health and healing through shared decision-making (Merenstein et al., 2005; Quinn et al., 2003). There has already been an enormous body of research in the area of the doctor-patient relationship (and more broadly, the health professional and patient) and the process of care (e.g., access, length, practice patterns, cost). There has also been substantial research in related areas such as social support (Cohen et al., 2001; Runyan et al., 1998); communication (Grinfeld et al., 2008; Langewitz et al., 2002); patient-centered care (Anderson et al., 2003; Mead et al., 2002); empathy (Bikker et al., 2005; Mercer and Howie, 2006; Mercer et al., 2008); effective ways of promoting behavior change (Barkin et al., 2008; Bell and Cole, 2008; McCambridge et al., 2008); different types of clinical encounters (e.g., individual versus group; in-person versus telephone or internet) (Hersh et al., 2001; McConnochie et al., 2006; Modai et al., 2006); patient satisfaction (Esch et al., 2008; Marian et al., 2008; Mermud et al., 2008); trust (Hall, 2006; Hall et al., 2002); and team-building and shared governance (Hope et al., 2005; Sierchio, 2003). To date, *little of this research on the processes of relationship-based care has been synthesized and integrated into the field of integrative medicine*. For example, research on acupuncture now often includes placebo needles, but has not examined closely the process of building the relationship between therapist and patient or compared the processes of care provided by acupuncturists with that provided by other practitioners; nor have comparisons been made about the relationships among team members on traditional medical multidisciplinary teams (e.g., clinician, nurse, social worker, physical therapist, occupational therapist) with integrative teams (e.g., naturopathic practitioners, nutritionists, acupuncturists, massage therapists).

### *Patient's Participation In Self-Care*

How to inspire, motivate, empower, and facilitate patient self-care is an important issue in integrative medicine. Self-care is a two dimensional construct that includes processes for health in self-care practice and action capabilities (Hoy et al., 2007). The processes include life experience, learning processes, and ecological processes. Action capabilities include power and performance capabilities.

The primary aim of inspiring, motivating, and empowering patients is towards a single goal—being able to bring about a positive behavior change. Several models have been developed to address behavior change. These include models based on attachment theory (Ciechanowski et al., 2001); the chronic care model (Bodenheimer et al., 2002); (Wagner, 1998); the extended parallel process model (Gore and Bracken, 2005); the health belief model (Champion, 1984; Jones et al., 1987); the problem solving model (Alley and Brown, 2002; Peter et al., 2006); the self management model (Price, 1993; Walker et al., 2003); social cognitive theory (Anderson et al., 2007; Hertz and Petosa, 2008); the transtheoretical model (Prochaska, 2006; Prochaska and Velicer, 1997); and the theory of reasoned action (Feeley, 2003; Hedeker et al., 1996). A common theme that emerges from a critical evaluation of all these models is that a planned intervention should ideally incorporate several essential components for successful behavior change. The two steps in this process involve assessment and action. Components of assessment include ascertaining the need for behavior change, resources, individual perception of need for change, and self efficacy. Most of these models were developed to address a specific medical condition. *There exists a need to test behavior change models within the context of multiple complex medical conditions that is representative of the patient population today.*

Comprehensive, integrative treatments recommendations, even for patients with a single diagnosis, involve lifestyle modifications as well as medications, resulting in *complex, multifaceted treatment plans* (Bell and Kravitz, 2008). Although most research on adherence has focused on medications, little is known about the impact of combining advice about medications with advice about other lifestyle factors on adherence to the pharmaceutical regimen. Lifestyle counseling appears to increase patient satisfaction, but its overall impact on cost of care and adherence is largely unknown (Harting et al., 2006; Johansson et al., 2005). Furthermore, adherence to specific recommendations may vary according to *patients' explanatory models* (Abraham et al., 2004). For example, patients who believe their hypertension is related to stress may be more adherent to recommendations about stress management, while patients who believe their blood pressure is purely a genetic or biochemical problem may be more adherent to pharmaceutical regimens (Hekler et al., 2008). Similarly, patients may invoke biochemical, genetic, personality, stress, cognitive, karmic, spiritual, environmental, weather-

related, astrological, or energetic explanations, or some combination of these factors for their symptoms and experiences. Different explanatory systems could have dramatically different impacts on patients' willingness to embark on or adhere to different treatment regimens. *Research on how to best match patients' explanatory models and disease pathophysiology with optimal treatment options and the impact of matching/mismatching on adherence, clinical outcomes, and satisfaction with care and cost of care is needed.*

### *The Global Village—Health Care And Societal Consequences*

Integrative medicine looks beyond individual health behaviors to larger *environmental, social, and educational* factors affecting health. Research has begun to establish the critical role of the environment on human health (Diaz, 2007; Johnson et al., 2008; Usta et al., 2008; Wilkinson, 2008). Research will play an important role in determining the *most effective, efficient, and equitable strategies for translating new knowledge about environment into integrative clinical practice*. Providing conventional *health care also impacts the environment* (e.g., pharmaceuticals contaminating drinking water supplies; biological and technical waste disposal; incineration of mercury, PVC, and other products) which in turn affects human health (Barnes et al., 2008a; Gaudry and Skiehar, 2007; Hiltz, 2007; Rabiet et al., 2006; Tudor et al., 2008; Zakaria and Labib, 2003). Integrative medicine explicitly attempts to provide care that is “green” and health promoting; the extent to which integrative care is more environmentally friendly than conventional care is unknown. Furthermore, there is strong evidence that stress adversely affects health; yet little research has addressed ways in which health care institutions can effectively improve their environment, reducing stress for both clinicians and patients. Finally, it is well known that social support mitigates against the pernicious effects of many stressors, and some hospitals (such as pediatric hospitals) have made efforts to improve family support (e.g., individual rooms allowing family members to remain with patients), yet there has been little systematic research on the most cost-effective strategies to improve social support for patients, family members, clinicians, or staff within health care institutions or the impact of such changes on health outcomes. *Research is needed to address ways in which integrative health care providers and institutions can reduce their adverse environmental impacts and promote positive healing environments while providing high quality affordable, effective, comprehensive care.*

Furthermore, advances in media, communication, commerce, and transportation technologies have resulted in well-documented changes in health behaviors (e.g., decreases in fruit and vegetable intake, increases in sedentary behavior); access to health information and misinformation; and access to health services (e.g.,

internet counseling, international travel for surgical procedures, telemedicine) (Breckons et al., 2008; Ebrahim et al., 2007; Houpt et al., 2007; Khazaal et al., 2008; Nava et al., 2008; Trotter and Morgan, 2008; Tsitsika et al., 2008), and professional education. Integrative medicine has been a leader in providing online courses (e.g., through the University of Arizona Center for Integrative Medicine) (Beal et al., 2006; Hadley et al., 2007; Kemper et al., 2006). *Research is needed to determine the most cost-effective and equitable strategies to provide integrative medicine and health education using modern telecommunications including telephone, internet, webinars, and teleconferences for both individual and group models.*

Social policies also profoundly affect health, and *integrative medicine, as a holistic discipline, must include research to better understand the impact of health policies on overall health.* For example, public energy policies that promote the use of coal-fired power plants (resulting in mercury-contaminated fish); agricultural policies that promote monocultures of corn, wheat, and soy (resulting in inexpensive and obesogenic diets); educational policies that rely on income from vending machines in schools (providing unhealthy nutritional options); school lunch programs (providing less than optimal nutrition); transportation policies that promote automobile rather than public transportation (increasing sedentary behavior as well as promoting global climate change); and zoning policies that promote sprawl all have important health consequences. Little research has been conducted to evaluate the health consequences of variations in social policies about agriculture, transportation, education, or energy. Such studies might include regional comparisons in the U.S. or comparisons of the effects of policy variations between countries and over time on broad health outcomes.

Also, public policies that affect payments for certain kinds of health care providers (e.g., MD, DO, DC) and a few kinds of therapy (e.g., prescription drugs and surgery) may have very different impacts on health outcomes, as compared to policies promoting payment for fitness club memberships, massage, and nutritional supplements. Little research to date has examined the effects of different reimbursement plans on health outcomes. Furthermore, most fee-for-service plans provide professional payments based on RVUs and DRGs, rather than on health outcomes (e.g., whether or not they help patients feel better or function more productively). Our reimbursement schemes favor short, repeated visits in which patient health does not necessarily improve. Research showing the benefits of certain kinds of care (e.g., patient-centered, good communication skills, stress reduction coaching, lifestyle coaching) in the absence of policies supporting their financial viability appear unlikely to be sustainable. *Thus, research is needed regarding the effective translation of knowledge about the environment and behavior into effective social policies and reimbursement schemes.*

## SETTING PRIORITIES FOR THE INTEGRATIVE MEDICINE RESEARCH AGENDA

### Framework to Set Priorities

Given the large number of research areas that need to be addressed and limited resources, a systematic approach to prioritizing projects is needed. A model has been proposed that includes attention to high priority conditions, populations, therapies, and a comprehensive view of important outcomes (Kemper et al., 1999).

#### *Conditions*

Priority should be given to conditions and diseases that satisfy the criteria in Table 1: those that impose a heavy burden of suffering to patients and costs to society for which current therapies are insufficient and for which integrative approaches offer a reasonable likelihood of being helpful and are already in use. Examples include anxiety, asthma, attention deficit disorder, back pain, cancer, cardiovascular diseases, chronic and severe pain syndromes, depression, developmental disorders, insomnia, obesity/metabolic syndrome, recurrent respiratory infections, rheumatic and autoimmune disorders, and addictive disorders.

TABLE 1 Criteria for Conditions, Diseases, and Risky Health Behaviors with High Priority for Integrative Medical Research
Those that
Impose a heavy burden of suffering on individuals, families or the community either because of their <ul style="list-style-type: none"> <li>● severity</li> <li>● chronicity</li> <li>● prevalence</li> </ul>
And
For which current mainstream therapies are unacceptable or insufficient because of <ul style="list-style-type: none"> <li>● lack of proven efficacy</li> <li>● substantial side effects</li> <li>● cost</li> <li>● lack of availability</li> </ul>
And
or which integrative medicine offers a reasonable likelihood of being helpful based on <ul style="list-style-type: none"> <li>● proven safety in animal models</li> <li>● lengthy historical use or compelling results from case reports, case series, epidemiologic studies, case-control trials or cohort studies, or clear scientific rationale</li> </ul>
And
Which families and practitioners are already using integrative approaches

### *Therapies*

Therapies requiring additional professional intervention are also priorities for research because of the substantial costs associated with professional care. Thus, research on the effectiveness, safety, and costs of chiropractic, acupuncture, electroencephalographic biofeedback, hypnosis, or other mind-body techniques requiring licensed professional therapists should be high priorities (Vas et al., 2006; Wasiaak and McNeely, 2006; Thomas et al., 2005). CAM practitioners, including spiritual healers, who advocate abandoning conventional medical care (e.g., transfusions or immunizations) also require investigation into the scope of their effect on individual health practices and overall public health (e.g., increased rates of vaccine preventable illnesses). Research on interventions (e.g. certain natural products) that have already been supported by a substantial amount of preliminary data and are on the verge of definitive evidence for widespread clinical application should also enjoy priority, as such research is likely to be a high yield investment.

### *Types of Research Synthesis*

Given the often conflicting data from medical research studies, overviews and data synthesizing analyses are critically important for translating research into practice. The Cochrane Collaboration and others have made important contributions to this field over the last 10 years, and additional analyses providing specific guidance to practicing clinicians, policy makers, and researchers is needed (Dorn et al., 2007; Gagnier et al., 2006; Lawson et al., 2005; Pham et al., 2005).

### *Outcomes*

Outcomes include not only traditional measures of morbidity, mortality, cost of care, and patient satisfaction, but also the impact of care on family cohesiveness, cultural identity, spiritual beliefs, resilience, coping, and self-efficacy. The impact on the environment also should be considered. *Additional outcome measures may need to be developed to address the concept of health as optimal functioning rather than as the absence of disease and to address patient priorities, particularly when there are multiple co-existing priorities.*

**TABLE 2**  
**Outcomes of Interest in Research on Integrative Medicine**

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<b>Patient outcomes</b>
<ul style="list-style-type: none"> <li>• Mortality rates, years of life saved</li> <li>• Morbidity—physical, psychological, emotional and social symptoms; severity of illness</li> <li>• Health behaviors—dietary, exercise patterns; smoking, drinking, and drug use; unprotected sexual relations</li> <li>• Health care utilization, including self-care, CAM care, and conventional care</li> <li>• Satisfaction with care</li> <li>• Developmental milestones and behavior</li> <li>• Activities of daily living</li> <li>• Quality of life</li> <li>• Costs associated with care</li> <li>• Direct and indirect financial costs; opportunity costs of missed treatments; side effects—symptomatic and asymptomatic organ dysfunction, injuries, infection; adverse interactions with other therapies; X-ray and other toxic exposures</li> <li>• Social outcomes <ul style="list-style-type: none"> <li>◆ Days of work/school missed; delinquency, incarceration</li> </ul> </li> </ul>
<b>Family outcomes</b>
<ul style="list-style-type: none"> <li>• Days of work missed; out-of-pocket costs; impact on insurability</li> <li>• Psychosocial impact on families; emotional impact on sense of empowerment</li> <li>• Spiritual outcomes: coping, peace, serenity, harmony in relationships, a sense of meaning or purpose in life, self-efficacy, self-esteem.</li> <li>• Social outcomes: divorce, employment, bankruptcy</li> </ul>
<b>Community outcomes</b>
<ul style="list-style-type: none"> <li>• Sense of cohesiveness, cultural identity ; social capital</li> <li>• Cost to society, rate of malpractice suits</li> <li>• Environmental impact: cost of remedy to society, environment, (overharvesting of herbs leading to extinction; climate change; pollution)</li> </ul>
<b>Provider outcomes</b>
<ul style="list-style-type: none"> <li>• Provider satisfaction with role</li> <li>• Burnout</li> <li>• Sense of effectiveness and part of healing community</li> </ul>

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The following sections discuss specific areas of research for discussion in setting priorities.

### **Spectrum of Life Cycle**

Integrative medicine can be provided to patients across the demographic spectrum of age, gender, and race/ethnicity, and there may be disparities in the availability and quality of services to different populations (Demattia et al., 2006). Integrative care can also be provided for prevention, acute, and chronic illness as well as rehabilitation and palliation. Among the most vulnerable populations which have been least studied are children, adolescents, and patients suffering from genetic or congenital disorders. Other research populations that should be

considered as high priorities include women across the life cycle, not only during pregnancy and breast-feeding, but also through the different phases of the menstrual cycle, at menarche and through menopause (particularly during pregnancy and breastfeeding periods), the frail elderly, patients with complex conditions and multiple comorbidities, patients at the end of life, those with limited access to care, and patients from diverse cultural/ethnic backgrounds. It is also important to study gender differences of the various interventions, not only in women, but also the differential effects of these interventions in men and women.

### **Epidemiological Studies**

With the development of large integrative clinics at medical institutions across the country, epidemiological methods can be used to generate novel data. A number of these institutions have begun collecting outcomes data on their patients to allow for prospective studies of integrative medicine, “The Outcomes Research Project” (Sierpina, 2008). In addition to outcomes data, it would be useful for these clinics to create registries of their patients to gather data on the specifics of the integrative treatments received by each patient. In order to conduct controlled cohort studies, it is essential that these centers identify an appropriate source of control patients whose use of CAM therapies and the use of integrative medicine clinics has been documented. If existing patient registries (such as the Cystic Fibrosis Foundation Patient Registry or the National Cancer Institute’s Surveillance, Epidemiology and End Results Program) systematically collected data on integrative medicine, they could provide an excellent source of data for cohort studies to compare the benefits and/or risks of integrative medicine.

Another type of research that should be encouraged in the field of integrative medicine is health services research (Coulter and Khorsan, 2008; Herman et al., 2006). Descriptive studies are needed to determine how providers practice integrative medicine, what patients seek care from integrative medicine clinics, the benefit patients receive from integrative medicine, and the cost effectiveness of integrative medicine (Cardini et al., 2006; Coulter and Khorsan, 2008; Fonnebo et al., 2007; Herman et al., 2006). Some researchers suggest that before conducting studies of efficacy of individual components of integrative medicine, pragmatic research should demonstrate the effectiveness of this medicine in the real world setting. If the system of integrative medicine is found to be effective, future studies can then examine the components of the whole system to determine if they are efficacious individually or only in combination. Individual components found to be efficacious could be further explored to determine their biological mechanism (Coulter and Khorsan, 2008; Fonnebo et al., 2007).

Finally, epidemiological studies would be wise to gather data about CAM use. Some forms of CAM use may confound findings of cohort and case-control studies. Several large meta-analyses have documented that individual vitamins can impact all causes of mortality (Autier and Gandini, 2007; Melamed et al., 2008; Miller et al., 2005; Omenn et al., 1996). Examining the possible confounding effects of these treatments is not possible if the data are never collected by researchers. Use of CAM therapies also needs to be studied for clinical research participants in order to decrease risks of interactions (Welder et al., 2006).

### **Basic Science, Mechanistic Studies**

The value of basic science research in integrative medicine lays in its ability to increase knowledge and understanding of how fundamental biological processes work. Some argue that the danger of taking the molecular approach to the extreme loses sight of the complex, interactive nature of human diseases and behaviors. Integrative medicine researchers should guard against this. On the other hand, basic science research is essential to elevate the level of research and broaden the impact of integrative medicine.

Among the areas which should be considered as priorities are the following:

- 1) Genomic/proteomic/pharmacogenetic studies investigating the individuality of patients despite sharing the same disease process. Such knowledge can be used to develop a personalized health care approach to disease prevention and treatment;
- 2) System biology studies to identify and characterize the interactions between multiple components of the biological processes and the interactions between mind and body. Research in this area will create new appreciation of the interconnectiveness of various components in human health and lead to therapeutic strategies that take advantage of such knowledge; and
- 3) Research on how behavioral interventions can change biological processes at the molecular and cellular level. This would create more effective tools for further behavior modifications relevant to reversing human diseases.

### **Diagnostic Techniques**

An area in need of further research is a critical assessment of the many novel laboratory assessments intended for evaluation of biomarkers indicative of disease risk, prognosis, or treatment options. Because of the novelty of these tests, little or

no data exists about their sensitivity and specificity, making interpretation of results difficult. In some cases, the tests offered are not diagnostic but rather informative of the individual, with their clinical meaningfulness unknown. In these cases, detailed information on the calculation of the normal ranges is often lacking in the test descriptions. Some novel laboratory tests may become the new standard of diagnosis or tool for monitoring effectiveness of treatment. However until more research documents their validity and reliability, these tests will continue to be considered experimental.

## **Clinical Interventions**

### *Study Design*

The paradigm of pragmatic (effectiveness) vs. explanatory (efficacy) studies is still relevant today, particularly in integrative medicine (Gartlehner et al., 2006; Schwartz and Lellouch, 1967). The pragmatic nature of a larger RCT, even one with few restrictions for enrollment, however, is still limited since the complex variables that go into individual decision making often cannot be controlled in clinical trials setting (Karanicolas et al., 2008). For research to be integrative, it will be important to define the real world contexts in which the results are to be applied. Another important issue here is the selection of appropriate outcome measures. Wherever possible, patient relevant variables should be included in pragmatic trials, not just surrogate outcome measures (Montori et al., 2007). The basic elements of study design and conduct need to be addressed adequately (Bloom et al., 2000). Even with a good study design, a single neglected issue could seriously impact the validity of the results (Pittler and Ernst, 2004). For research to have a meaningful impact on integrative patient care, the investigator should focus on conducting well-designed studies with minimal bias, keeping particular aspects of the intervention in mind, while also being mindful of the appropriate stage of research (pragmatic vs. explanatory).

### *Personalized and Holistic Health Care*

In keeping with the goal of patient-centered holistic care in integrative medicine, future research should consider going beyond studying individual modalities for specific disease indication. In a holistic view, many human diseases are connected through hub processes underlying the pathological processes. Some of these processes have been identified, others have not. This connection has been underappreciated in a reductionist research approach, but quite commonly re-

flected in the narratives of many traditional medical systems. Systems biology research has shown that one possible mechanism of such “human disease network” is shared disorder-gene associations (Cusick et al., 2005). A bipartite human metabolic disease association network has been created in which nodes are diseases and two diseases are linked if mutated enzymes associated with them catalyze adjacent metabolic reactions (Lee et al., 2008). The model shows *a network topology for disease comorbidity* (Goh et al., 2007). Integrative medicine research can similarly use mathematical models to explore other such connections based perhaps not on genes, but on other functional variables (Bell and Koithan, 2006; Verhoef et al., 2005; Verhoef et al., 2006b).

To emphasize patient-centered care, future integrative medicine research should take advantage of technological advancements to individualize intervention and outcome assessment (Snyderman and Langheier, 2006). Application of pharmacogenetics knowledge to herbal medicine trials may result in a better selection of the study population, hence reduce sample size and increase the effect size, leading to more efficient use of research resources and minimizing the number of falsely negative trials (Arab et al., 2006; Fernandes, 2008). Computerized patient-centered outcomes assessment networks would produce efficacy endpoints. These endpoints should take into consideration patients’ priorities in wellness, be more clinically relevant, and be consistent with the goal of integrative medicine (Kaasa et al., 2008).

Patient expectations and beliefs about therapies are intricately linked to their explanatory models and sense of meaning (Cohen, 2003; Di Blasi et al., 2001). New methods and tools are being devised to assess patients’ beliefs and attitudes, but these have not been widely implemented (Dennehy et al., 2002; Lewith et al., 2002; O’Callaghan and Jordan, 2003). Similarly, different practitioners’ expectations, beliefs, values, and explanatory models are likely to affect the kinds of diagnostic evaluations, counseling, and treatments offered to patients (Armbruster et al., 2003; Curlin et al., 2007; Saal, 2002). In addition, patients may have different values and priorities in addressing their symptoms, and attention to these priorities may affect satisfaction with care and adherence to recommendations (Ammentorp et al., 2005). For example, different patients who have hypertension, allergies, insomnia, anxiety, and chronic pain may have different priorities for treatment—one may focus on hypertension while another may be more focused on pain or insomnia or anxiety. The same patient may have different priorities at different times or when accompanied to the visit with different family members who are affected by the patient’s condition.

*The complex issues inherent in providing patient-centered integrative care in the context of multiple conditions in patients with different priorities, values, expectations, and beliefs are poorly understood. It is possible that new research paradigms will be needed to address this lack of knowledge, not only for clinical*

*outcomes, but for satisfaction with and cost of care for patients, as well as the impact on practitioners (e.g., burnout and fatigue) and the public's health (e.g., overall health care costs, impact on work/school, activities of daily living).*

### *Promoting Self Care and Individual Resilience*

To encourage behavior changes and promote self care, the planned integrative action has to be multi-dimensional. Optimal use of skills in motivational interviewing for patients in the pre-contemplative or contemplative stages is likely to help (Hettema et al., 2005). Mind-body interventions that are likely to help develop resilience include mind-body modalities such as relaxation, hypnosis, visual imagery, meditation, yoga, tai chi, qi gong, cognitive-behavioral therapies, group support, autogenic training, and spirituality. In addition to these approaches, cultivating compassion, forgiveness, gratitude, and finding meaning and purpose to one's life are also important towards developing contentment and happiness and thus fostering resilience (Brass et al., 2003; Farrow et al., 2001). Optimal disease management, nutrition, physical exercise, and restorative sleep are also likely to foster resilience. Interventions primarily aimed to foster resilience are beginning to be tested in clinical trials. These studies mostly show promising results and have involved patients with diabetes (Bradshaw et al., 2007), are conducted as work site interventions (Waite and Richardson, 2004), include college students with academic stress (Steinhardt and Dolbier, 2008), or take place in school settings (Ruini et al., 2006). Early studies suggest that resilience might correlate with selective activation of the left prefrontal cortex (Davidson, 2000). This needs to be further validated. *Integrative models for behavioral change need to be developed and tested to motivate patients with multiple complex medical problems for a sustained change in behavior. Research into designing and testing resilience interventions incorporating the wisdom of alternative healing systems and further understanding the neurobiology of resilience has the potential to transform patient care.*

### *Practitioner-Patient Interaction and Partnership*

A more integrative approach towards patient care entails incorporating biopsychosocial interdisciplinary content emphasizing compassion, communication, mindfulness, respect, and social responsibility (Wear and Castellani, 2000). A core aspect of integrative medicine is the importance of the *relationship* between practitioner and patient (Chang et al., 1983; Quinn et al., 2003) that has been incorporated into the evolving concept of "relationship-centered care." Relation-

ship-centered care focuses on the importance of human relationships with experience of the patient being at the center of care. The onus of initiating this process rests on the practitioner. The two key skills for the practitioner to facilitate this form of care are to cultivate professionalism and humanism (Klein et al., 2003). *The impact of training clinician healers is beginning to be investigated (Miller et al., 2003; Novack et al., 1999) and is a ripe area for future research in integrative medicine.* Such an approach is likely to enhance the nonspecific therapeutic effect of a medical encounter.

In a clinical trial, patients improve for multiple reasons. These include spontaneous remission, natural course, regression to the mean, biased reporting, nonspecific therapeutic effects, and specific therapeutic effects. The nonspecific therapeutic effect, which may account for improvement in up to 60 percent of patients for some conditions (Kaptchuk et al., 2008), has been considered more a nuisance than a useful therapeutic effect because of the need to control within the context of placebo-controlled trials for pharmacologic treatments. However the efficacy observed in the placebo arm may sometimes be significantly superior to no treatment or standard medical care (Brinkhaus et al., 2006; Haake et al., 2007; Linde et al., 2005; Melchart et al., 2005). The skills of professionalism and humanism within an integrative encounter are likely to increase this nonspecific effect.

Instead of considering the placebo effect as of secondary importance, it might be more apt to consider the placebo effect as "contextual healing," an aspect of healing that has been produced, activated, or enhanced by the context of the clinical encounter (Miller and Kaptchuk, 2008). Variables that maximize contextual healing include the environment of the clinical setting, cognitive and affective communication of practitioners, and the ritual of administering the treatment (Kaptchuk, 2002). *Integrating research efforts towards harnessing the nonspecific therapeutic effect rather than controlling for it is likely to offer expanded tools and additional insight into patient care. In situations where it is important to separate the specific effect from "contextual healing," optimal effort needs to be placed towards validating a placebo control prior to pursuing large multi-center trials.*

## RECOMMENDATIONS FOR ACTION

The ultimate goal of integrative medicine research is to guide clinical practice, thereby maximizing benefit and minimizing patient risks. When formulating clinical guidelines, two factors are in play: strength of evidence and burden/risk to the patient. Because it is not always possible to have definitive evidence on safety and effectiveness and clinical decisions have to be made with limited information,

burden and risk to the patient need to be taken into account. Although the highest level of evidence is desirable for every health intervention, it is simply not possible to achieve this goal. Limited research resources have to be allocated according to priorities. Therefore, interventions or therapies with high risk or burden (economic/time/effort) to patients and society must meet a high standard in strength of evidence, often in the form of multiple RCTs, to be utilized in clinical practice. Those with low or little risk/burden can be incorporated into practice even when the highest level of evidence is not available (McCrorry et al., 2007). Such an approach can be summarized in a simple 2x2 table (Table 3) about how to decide whether or not to use a particular therapy based on safety and effectiveness. Implicit in this model is the notion that the clinician and patient both understand and agree on the problem; the goal of therapy; the evidence regarding safety and effectiveness of the therapy being considered; the extent to which it is accessible, affordable, and of high and consistent quality; and availability of similar information about alternative treatments (or a combination of treatments) under consideration.

In light of this relationship between research and clinical practice and the issues discussed in Sections on Context and on Setting Priorities, we make the following recommendations for action regarding integrative medicine research. We suggest the actors for each recommendation be discussed at the IOM Summit on Integrative Medicine and the Health of the Public. Key stakeholders need to be identified to make it a collaborative, multidisciplinary effort for each item—including researchers, patients, and policy makers.

1. Identify pressing areas of research in integrative medicine and define the level of evidence required for their clinical applications.
2. Establish a consortium of integrative medicine researchers to form consensus on how to implement the research priorities as follow-up to this summit.
3. Build an international information technology platform which standardizes and facilitates data acquisition, data banking, and communication between researchers to achieve synergy of productivity.
4. Demonstrate the value of integrative medicine in health maintenance and disease prevention to policy making bodies, especially in light of the current economic setting of burgeoning health care cost to society, so that more resources can be allocated to integrative medicine research.

**TABLE 3** Benefit and Risk Ratio and Selection of Therapies

		<b>EFFECTIVE</b>	
		YES	NO
<b>SAFE</b>	YES	USE	TOLERATE
	NO	MONITOR	AVOID

We propose the following questions to be discussed during the summit.

1. What are the three most important research questions in integrative medicine as a whole?
2. What should be the top three research priorities in integrative medicine in the setting of limited research resources?
3. What progress would you like to see made in integrative medicine research in the next 3-5 years?

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